

REMARKS

No new matter is added by way of the amendments.

Claims 1-16 are pending in the application. Claims 8-14 stand withdrawn pursuant to a Restriction Requirement made Final in the Office Action mailed July 18, 2003.

Claim 3 has been amended to place it into independent form by inserting the recitation of claim 1 into claim 3. New claims 15 and 16 have been added. Claims 15 and 16 are supported by original claims 6 and 7.

Withdrawn Objections and/or Rejections

Applicants note with appreciation that the objections to the specification are withdrawn.

Applicants note with appreciation that the objection to claim 4 is withdrawn.

Applicants note with appreciation that the rejection of claims 1-7 under 35 U.S.C. § 112, second paragraph is withdrawn.

Rejection of Claims 1-7 under 35 U.S.C. §112, first paragraph

Claims 1-7 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The claims contain subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

Claim 1 (as amended) now recites methods for treating a disorder characterized by dysregulation of the GH/IGF axis in a mammal by administering to a mammal an effective amount of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of the native sequence human IGF-I are replaced with an alanine, a glycine or serine residue. Claim 3 (as amended) now recites a method for treating a renal disorder by administering to a mammal an effective amount of an IGF-I variant wherein the amino acid residue at position 16, 25,

or 49 or the amino acid residues at positions 3 and 49 of the native sequence human IGF-I are replaced with an alanine, a glycine or serine residue.

The Patent Office states that the term "disorder characterized by dysregulation of the GH/IGF axis" in the claims is interpreted to be broad in that it encompasses any and all diseases or disorders involved in the regulation of anabolic and metabolic homeostasis. The specification allegedly does not teach treating any disorder characterized by dysregulation of the GH/IGF axis in a mammal by administration of any IGF-I variant. Undue experimentation allegedly would be required of the skilled artisan to determine the optimal quantity, duration and route of administration of an IGF-I variant. Overall, the specification allegedly does not teach the treatment of any disorders by any IGF-I variants, particularly the double mutants.

Applicants have amended claim 3 so that it is an independent claim and it recites treating a renal disorder. Claim 3 does not recite the term "disorder characterized by dysregulation of the GH/IGF axis". Claims 4 - 5 and 15-16 depend from claim 3. Applicants believe that this amendment renders this rejection moot with regard to claims 3-5 and 15-16. Withdrawal of this rejection for claims 3 - 5 is respectfully requested.

Applicants maintain that there is sufficient disclosure in the specification to be enabling for claims 1-7.

The amount of disclosure required to be supplied by an enabling specification has been discussed and defined in court decisions. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); see also Amgen Inc. v. Chugai Pharms. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991). "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is undue" In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). "Enablement is not precluded by the necessity for some experimentation ... [the] experimentation needed to practice the invention must not be undue experimentation." Enzo Biochem, Inc. v. Calgene, Inc. 188 F.3d 1362, 1371 (Fed. Cir. 1999).

The initial burden is on the Patent Office to provide a reasonable explanation of why the specification does not enable the scope of the protection claimed. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidenced sufficient to convince such a person of the invention's asserted utility. In re Brana, 51 F3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995)

The PTO has not met its burden. The PTO has not identified specific reasons why the IGF-I compounds of the present invention are not enabled. The patent office agrees that the claimed method may utilize routine administration and agent formulation techniques. The patent office merely states that the results of the method are unpredictable and complex when combined with the step of administering the claimed IGF-I variant to treat the clinical manifestations of any disorder characterized by dysregulation of the GH/IGF-I axis. The patent office does not offer any reasons why the variants would not work in the claimed method. Absent such proof, the patent office has not met its burden and this rejection should be withdrawn.

Applicants, in the specification, have defined disorders "characterized by dysregulation of the GH/IGF axis" in the specification at, for example, page 11, line 23 to page 12, line 3 as being "characterized by defects in growth, physiology, and/or glycemic control and those with clinical manifestations of either IGF excess or deficiency and/or GH resistance and/or deficiency, the latter being manifested by reduced levels of IGFBP-3 and/or increased levels of IGFBP-1" (emphasis added). The specification then provides a number of diseases "characterized by increased IGFBP levels (such as IGFBP-1) relative to such levels in a mammal without the disorder" (emphasis added). See page 11, lines 29-35. Accordingly, the disease states are characterized by a common biochemical profile. Determination of increased IGFBP-1 levels and reduced IGFBP-3 levels can be done through standard clinical means, for example ELISA for levels of molecules, clinical chemistry RIA or bioassay. Thus, one skilled in the art based on the disclosure in the specification would understand what is meant by the phrase 'diseases characterized by dysregulation of the GH/IGF axis' that

make it possible to treat such clinical manifestations by the IGF-I variants of the invention.

Further, Applicants describe precisely the IGF-I variants of the claimed invention and show that the variants bind IGFBP-1 very weakly while retaining high affinity binding of IGFBP-3. See for example, Example 1, page 27-38. and Tables I and II. The binding affinities of the double mutants are shown in Example 2, Table III, pages 38 - 42. Example 2 shows that the variants have significantly reduced binding affinities for IGFBP-1 but retain the same binding affinity to IGFBP-3 as the wild-type IGF-1. Example 2 further describes the KIRA assay of IGF-I type receptor activation and shows that the variants maintain the ability to activate the IGF-I receptor. Therefore the variants are fully biologically active. Example 2 also shows that the variant F49A and the E3A.F49A double mutant accumulate at higher levels in the kidneys of rats compared to wild-type IGF-I. The specification states that this would be beneficial for renal failure.

In addition to this example and to the teachings discussed by the Examiner, Applicants respectfully note that the specification provides a significant amount of disclosure describing how to practice the invention. For example, further disclosure related to **treatment methods** may be found, for example, at pages 21 –26. **Modes and methods of administration** are discussed, for example, at page 21, lines 26-33; page 23, lines 20-32; page 25, lines 4-34 and page 26, lines 1-13. **Formulation of pharmaceutical compositions** including IGF-I variants are discussed, for example, at page 24, lines 1-35. **Dosages and methods of determining effective dosages** are discussed, for example, at page 22, lines 11-32, detailing what is, and how to determine, an effective amount of an IGF-I variant. **Treatment regimens** are discussed, for example, at page 23, lines 13-17. Other particulars regarding **alternative delivery methods** (e.g., page 23, lines 20-34) and **modes of preparation and storage** (e.g., page 24, lines 30-35 and page 25, lines 1-3) are also disclosed in the specification.

It is known that IGFBP-3 is a GH-dependent protein and is reduced in cases of GH deficiency or resistance. It is known that the levels of IGFBP-3 are positively

regulated by IGF-I, See page 37, lines 27-29. On the other hand, IGFBP-1 is an inhibitor of IGF-I activity and is increased in most cases of GH-resistant states such as diabetes and renal failure, etc. Page 4, lines 21-26. Use of wild-type IGF-I to treat mammals suffering from kidney disorders, renal dysplasias, and /or renal hypoplasias is described in U.S. Patent No. 5,985,830. Intermittent administration of IGF-I to treat chronic disorders such as chronic renal failure, AIDS associated cachexia and type II diabetes is shown in U.S. Patent No. 5,565,428 and 5,741,776. These patents are referenced in the background section of the specification. U.S. Patent No. 5,565,428 and 5,741,776 teach various methods of administration and dosages of wild-type IGF-I to treat human patients. Accordingly, an IGF-I mutant with a reduced affinity for IGFBP-I without loss of ability to bind to IGFBP-3 could be administered by these methods and would be an effective therapy for these clinical conditions.

The Examiner has indicated that Example 3 does not teach the administration of the claimed IGF-I variant to humans. Example 3, entitled "Treatment of Humans" discloses how recombinant human IGF-I was administered to Type II diabetes patients to treat the disease. Applicants maintain that the claimed variant IGF-I could be administered to humans by the same method disclosed in Example 3 or by the methods described in U.S. Patent No. 5,741,776. The Patent Office has not provided any reasons why the variants of the present invention could not be administered in this fashion.

The Patent Office argues that the Applicants have not shown that all possible disorders characterized by dysregulation of the GH/IGF-I axis can be treated by the IGF-I variants. Applicants maintain that this is not the proper test. The courts have held that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental models is sufficient to establish utility". In re Brana 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) citing In re Krimmel 292 F2d 948, 953, 130 USPQ 215, 219 (CCPA 1961). In this case the Applicants have shown that the variants possess biological activity with reduced binding affinity for IGFBP-I. It was known in the art that wild-type IGF-I can be used to treat disorders characterized by dysregulation of the GH/IGF-I axis. It is reasonable that the variants of the present

invention, given their properties, can be used to treat disorders characterized by dysregulation of the GH/IGF-I axis.

For the above reasons, Applicants maintain that their specification is fully enabling for the claimed invention. Withdrawal of this rejection is respectfully requested.

The Rejections to Claims 1-7 under 35 U.S.C. §112, second paragraph

Claims 1-7 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The term "clinical manifestations" in claims 1-7 is a relative term which allegedly renders the claims indefinite. The Patent office indicates that although page 8 and 11 of specification provides support for the term, the limitations in the specification will not be read into the claims. The claims must independently define the invention.

Applicants have deleted the objected term from Claim 1. This amendment serves to clarify the claim language but does not narrow its scope. Accordingly, this rejection is rendered moot and withdrawal of this rejection is respectfully requested.


CONCLUSION

For the reasons set forth above, Applicants believe that all claims are in condition for allowance. Should the Examiner believe that a telephone interview would expedite the prosecution of this application, Applicants invite the Examiner to call the undersigned attorney at the telephone number indicated below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** referring to Attorney's Docket No. **39766-0131 R1-1D1**.

Respectfully submitted,

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